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CHANG, CELIA C	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/928,139
Filing Date: August 10, 2001
Appellant(s): LANGSTON ET AL.

Doran R. Pace
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed Mar. 8, 2005.

5-0-0

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient.

A careful comparison of GB 9602174.6 (priority document **1**, priority date 02 Feb. 1996), GB 9618836.2 (priority document **2,** priority date 10 September 1996), US 60/021,135 (priority 3, priority date 112 September 1996) parent case 08/792,415 and the instant specification amended 10 August 2001 resulted in the following observation:

Priority document 1 (exhibit A)

On page 1, last paragraph it was disclosed "This invention is based on the novel discovery of methods to effect **epimerization** of *both* chiral centres in methylpyenidaate. Such epimierzation gives a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer** which can then be reinput into the resolution" Scheme 1 was delineated.

On pages 2 and 3, mechanism, steps and structures were delineated in scheme 2 and 3 using ***l-threo***-methylphenidate being the "unwanted" isomer as the starting material of the racemization/recycle process (see starting material of schemes 2 and 3, also claims 1-14, p. 4).

Priority document 2 (exhibit B)

On page 1, lines 18-19, it was described that "In general, it is the *d-threo* [or (R,R)] enantiomer that is considered to have the preferred therapeutic acitivity." (i.e. the wanted isomer)

On page 2, lines 5+ it was disclosed "This invention is based on the novel discovery of methods to effect **epimerization** of *both* chiral centres in methylpyenidaate. Such epimierzation gives a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer** which can then be reintroduced into the resolution" Scheme 1 was delineated.

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On page 4 and 5, an example using *d-threo* methylphenidate (wanted isomer) with propionic acid and refluxed in toluene to obtain all 4 stereoisosmers of methylphenidate in roughly equal proportions was disclosed at this time.

Instant application specification

On page 2, lines 8-9, it was disclosed that "The invention is based on the discovery of methods to effect *racemization* of both chiral centeres of methylphenidate. This process gives an optically inactive mixture of stereoisomeers in which equilibrium may favour the *threo* isomer.....predominantly into the racemate of the threo isomer which can be reintroduced into the resolution"

On page 3, line 26-31, it was disclosed that "As indicated above conditions are known that will epimerize *erythro* ritalinic acid at the.....that conditions can be adopted in order to give all 4 stereoisomers of methyl phenidate by racemization at both chiral center" and "following racemisation, and prior to resolution, it is ***necessary*** to enrich the mixture in the *threo* enantiiomer"

on page 4, lines 12-24 it was disclosed that "In order to preparing *d-threo* methylphenidate by an efficient recycling.....suitable as a feedstock for resolution into constituent enantiomers"

Therefore, contrary to appellant's summary of invention:

--the first piority document disclosed an "epimerization" process using unwanted isomer (l-threo methylphenadine) to obtain a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer**.

--the second priority document disclosed the same invention as described in the first priority document, further disclosed an example of using *d-threo* methylphenidate (wanted isomer) with propionic acid and refluxed in toluene to obtain all 4 stereoisosmers of methylphenidate in roughly equal proportions.

--the instant application disclosed "epimerize *eythro*-isomer" to obtain all four stereo isomer which is necessary to enrich the mixture in the threo enantiomer"

Please note that claim 1 of the appendix A is claiming "A process for obtaining single enantiomer of *d-threo* methylphenidate or *l-threo-* methylphenidate.....racemisation of the unwanted enantiomer to give a mixture of all four stereoisosmers.....to leave the said mixture of d-threo methylphenidate and l-threo methylphenidate enantiomers for resolution" was not disclosed in either priority document 1 or priority document 2 or the instant specification. This claimed invention can not be grnated priority benefit because:

For an epimerization/racemization process of an unwanted isomer (wherein only one unwanted isomer was described which is *l-threo* methylphenidate) to a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer** which can then be reintroduced into the resolution, such a process was described in priority documents 1 and 2 and the instant application. However, the instant claimed process starts with either d-threo or l-three, i.e. both desired isomer and undesired isomer to a recycle process, thus, the described invention was not the instant claim.

For a process of using the *d-threo* methylphenidate (the desired isomer) which was racemized with propionic acid and refluxed in toluene, to form *all four isomers in roughly equal propotion*. The priority benefit is limited to priority document 2. As it was explained above, this process was not the instant claim.

No where was a process of using *l-threo* methylphenidate or *d-threo* methyl phenidate in a racemization process to obtain **4** stereo isomers (in any quantitative relationship) were found.

The description of obtaining 4 stereo isomers in any quantitative relationship was describe in the instant specification using *erythro* methyl phenidate with an enrichment step to the *threo* mixture. But this process was not the instant claim.

Therefore, contrary to appellants' description that the instant invention is a process racemizing *d- or l-threo* methylphenidate to all four isomers without any quantitative limitation, the description and examples of the priority documents and instant specification described otherwise.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: the inadvertent omitted rejection of claim 1 under 35 § 112 first paragraph is hereby reiterated and the arguments submitted in the Appeal Brief filed July 19, 2004 are also reinstated.

(7) Grouping of Claims

The rejection of claims 1-8 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

4254261	Miller et al.	03-1981
5733756	Zeitlin et al.	01-1996
6121453	Zavarch	09-2000

Barry "Racemization of alpha-amino acid ester....." CA 119:73084 (1993)

Miller et al. "Racemization of 6-oxo-piperidine-carboxylic acid enantiomers" CA 94:47148 (1981)

Armstrong et al. Science vo. 232 p.1132-1135 (1986)

Gao et al. "Synthesis and separation of optically active compounds" Ann. Pharmaceutiques v. 52, p.184-203 (1994)

Beausoleil et al. "5-ter-butylproline" J. Org. Chem. v. 61, p.9447-9454 (1996)

Shimoju et al. "Preparation of DL erythro or DL threo phenylserine derivatives" CA 114:123080 (1991)

(10) Grounds of Rejection

Claim 1 is rejected under 35 USC 112 first paragraph for lack of description and enablement

The clear delineation and flow of description of the priority documents and the instant specification as found in section 5 showed the clear lack of description and enablement of the "claimed" invention. The limitation of producing all four isomer from the d- or l-threomer finds no antecedent basis or enablement. The rejection is the result of the delineation supra which is hereby incorporated:

A careful comparison of GB 9602174.6 (priority document **1**, priority date 02 Feb. 1996), GB 9618836.2 (priority document **2,** priority date 10 September 1996), US 60/021,135 (priority 3, priority date 112 September 1996) parent case 08/792,415 and the instant specification amended 10 August 2001 resulted in the following observation:

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racemate of the *threo* isomer which can then be reinput into the resolution" Scheme 1 was delineated.

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On page 4 and 5, an example using *d-threo* methylphenidate (wanted isomer) with propionic acid and refluxed in toluene to obtain all 4 stereoisosmers of methylphenidate in roughly equal proportions was disclosed at this time.

Instant application specification

On page 2, lines 8-9, it was disclosed that "The invention is based on the discovery of methods to effect *racemization* of both chiral centeres of methylphenidate. This process gives an optically inactive mixture of stereoisomeers in which equilibrium may favour the *threo* isomer.....predominantly into the racemate of the threo isomer which can be reintroduced into the resolution"

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Therefore, contrary to appellant's summary of invention:

--the first piority document disclosed an "epimerization" process using unwanted isomer (l-threo methylphenadine) to obtain a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer**.

--the second priority document disclosed the same invention as described in the first priority document, further disclosed an example of using *d-threo* methylphenidate (wanted isomer) with propionic acid and refluxed in toluene to obtain all 4 stereoisosmers of methylphenidate in roughly equal proportions.

--the instant application disclosed "epimerize *eythro*-isomer" to obtain all four stereo isomer which is necessary to enrich the mixture in the threo enantiomer"

Please note that claim 1 of the appendix A is claiming "A process for obtaining single enantiomer of *d-threo* methylphenidate or *l-threo-* methylphenidate.....racemisation of the unwanted enantiomer to give a mixture of all four stereoisosmers.....to leave the said mixture of d-threo methylphenidate and l-threo methylphenidate enantiomers for resolution" was not disclosed in either priority document 1 or priority document 2 or the instant specification. This claimed invention can not be grnated priority benefit because:

For an epimerization/racemization process of an unwanted isomer (wherein only one unwanted isomer was described which is *l-threo* methylphenidate) to a theromodynamic mixture of isomers and given that the equilibrium favours the *threo* isomer, the result is that undesired enantiomer is converted **predominantly into the racemate of the *threo* isomer** which can then be reintroduced into the resolution, such a process was described in priority documents 1 and 2 and the instant application. However, the instant claimed process starts with either d-threo or l-three, i.e. both desired isomer and undesired isomer to a recycle process, thus, the described invention was not the instant claim.

For a process of using the *d-threo*_methylphenidate (the desired isomer) which was racemized with propionic acid and refluxed in toluene, to form *all four isomers in roughly equal propotion*. The priority benefit is limited to priority document 2. As it was explained above, this process was not the instant claim.

No where was a process of using *l-threo* methylphenidate or *d-threo* methyl phenidate in a racemization process to obtain **4** stereo isomers (in any quantitative relationship) were found. The description of obtaining 4 stereo isomers in any quantitative relationship was describe in the instant specification using *erythro* methyl phenidate with an enrichment step to the *threo* mixture. But this process was not the instant claim.

Therefore, clear evidence indicated what was disclosed was not identical to what was claimed. The lack of description and enablement of the "claimed" invention is clearly documented.

While the supportive invention of employing the "unwanted" isomers with racemization to the naturally thermodynamically equilibriumed mixture of all four isomers is established to be prima facie obvious in the rejections below; the invention encompassed by the claims using the wanted isomer to form the thermodynamically equilibriumed mixture or using the unwanted isomers to form the *all four isomer in roughly equal amounts* finds no description nor enablement in the specification or the priority documents.

Claims 1-8 are rejected under 35 USC 103(a) or obviousness type double patenting

(a) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8, to the extend that the process is for making *d-threo* methylphenidate, using the unwanted *l-threo* methylphenidate, to produce an optically inactive mixture of stereoisomeers in which equilibrium may favour the *threo* isomer.....predominantly into the racemate of the threo isomer which can be reintroduced into the resolution, these claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeitline et al. US 5,733,756 or Armstrong et al. Science in view of Miller CA 94, Barry CA 119 or Miller US 4,254,261.

Determination of the scope and content of the prior art (MPEP §2141.01)

Zeitline '756 or Armstrong et al. disclosed processes for making a single enantiomer of d-threo-methylphenidate or l-threo-methylphenidate from racemic mixtures. See Zeitline '756 col. 6-7, example 5, and col. 6, example 4 wherein both acid or ester can be used to obtain the single isomer. See Armstrong's whole article with methylphenidate exemplified on page 1133 last compound of table 1.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Zeitline or Armstrong disclosed all the elements of the claims **except** wherein a recycle by racemization step was not included. Barry taught that in preparation of amino acid esters (please note that the instant methylphenidate is a cyclic amino acid ester) analogous to the claims, racemization is achieved under acidic conditions and the analogous art by Miller (CA 94) or '261 taught that recycling the racemized isomers would give more of the intended isomer (see Miller's abstract and '261 col. 1 lines 64-66). In addition, both heat and acid were taught by the prior art as agents for racemization (see Barry and Miller).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing yield of a single isomeric form in the possession of an artisan in the field. It would have been prima facie obvious to employ a conventional modification of recycle/racemization step for the conventional process of Zeitline or Armstrong **because** producing higher yields of a desirable single isomer is expected, and such expectation is the attributes taught by the prior art. The teaching of Zeitline that either a free acid or ester can be separated suggested to one skilled in the art that a racemization step can be either before or after esterification.

(b) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, to the extend that the process is for making *d-threo* methylphenidate, using the unwanted *l-threo* methylphenidate, to produce an optically inactive mixture of stereoisomeers in which equilibrium may favour the *threo* isomer.....predominantly into the racemate of the threo isomer which can be reintroduced into the resolution, these claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeitline et al. US 5,733,756 or Armstrong et al. Science in view of Miller CA 94, Barry CA 119 or Miller US 4,254,261 further in view of Harris Us 6,242,464.

The rejection of claims 1-6 and 8 over Zeitline et al. US 5,733,756 or Armstrong et al. Science in view of Miller CA 94, Barry CA 119 or Miller US 4,254,261 is also applicable here and incorporated by reference.

The limitation of claim 7 is also conventional since the same compound and the same reagent have been used in purifying the enantiomer as claimed, see the whole article of Harris.

(c) Claims 1-8, to the extend that the process is for making *d-threo* methylphenidate, using the unwanted *l-threo* methylphenidate, to produce an optically inactive mixture of stereoisomeers in which equilibrium may favour the *threo* isomer.....predominantly into the racemate of the threo isomer which can be reintroduced into the resolution, these claims are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,121,453 in view of Miller CA 94, Barry CA 119 or Miller US 4,254,261 further in view of Harris Us 6,242,464.

Determination of the scope and content of the prior art (MPEP §2141.01)

Zavarch claimed a processe for making a single enantiomer of d-threo-methylphenidate or l-threo-methylphenidate from racemic mixtures. See claim 1.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Zavarch claimed a similar process with all the claimed elements **except** wherein a recycle by racemization step was not included. Barry taught that in preparation of amino acid esters (please note that the instant methylphenidate is a cyclic amino acid ester) analogous to the claims, racemization is achieved under acidic conditions and the analogous art by Miller (CA 94) or '261 taught that recycling the racemized isomers would give more of the intended isomer (see Miller abstract and '261 col. 1 lines 64-66). In addition, both heat and acid were taught by the prior art as agents for racemization (see Barry and Miller).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing yield of a single isomeric form in the possession of an artisan in the field. It would have been prima facie obvious to employ a conventional modification of recycle/racemization step for the issued co-owned claim 1 of Zavarch **because** addition of a recyle/racemization step to produce higher yields of a desirable single isomer is expected, and such expectation is the attributes taught by the prior art. In the absence of unexpected results, the instant claims are an unreasonable prolonging of exclusive rights by the addition of prima facie obvious steps to the process.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(11) Response to Argument

(A) 35 USC 119 (a) sets forth that granting of benefit of foreign priority filing date to applications which have the "same" invention as the priority documents for which a claim of

priority benefit was made. As it has been clearly delineated in section 5 of the content, description and claims of the priority documents, the instant claims can not be granted of the priority benefit since such "same" invention was not identified.

Appellants argued that all through the priority documents the process of racemization and sheme 2 of the documents showed the racemization starting with and "unwanted" enantiomer of methylphenidate is erroneous. As it was clearly identified by pages and lines,:

----the priority documents disclosed *l-threo* being the unwanted starting material while the instant claims is either *l-threo* or *d-threo*, i.e. different starting material.

----the product of the racemization of the "unwanted" *l-threo* is a thermodynamic mixture of stereoisomeers in which equilibrium may favour the *threo* isomer, the result is that undesired enantiomer is converted predominantly into the racemate of the threo isomer which can be reintroduced into the resolution. Please note that the claims are drawn to process for making "all four isomer" for which no quantitative relationship was identified.

----the priroty documents disclose that in racemizing the *d-threo* isomer, a *thermodynamic* mixture of stereoisomeers in which equilibrium may favour the *threo* isomer, the result is that undesired enantiomer is converted predominantly into the racemate of the threo isomer, i.e. no need to any enrichment step, while the instant claims require the step of "enriched over". The priority documents actually teaches away from the instant claims since the thermodynamic result is innate nature to the process with the need for any enrichment.

Just because all priority documents and the instant claims used enantiomer and racemization does support the "same" invention since the starting material is different, the product is different, the steps are different i.e. different invention.

(B) Initially, it is noted that applellants presented that Harris '464 reference should be under the 103(c) condition, thus, is not prior art. Although the examiner tried to keep track of the assignment, the continuous changing in assignment information made it very difficult. However, please note that the status of the Harris '464 reference is only applicable to claim 7. The 103(a) rejections over claims 1-6 and 8 which do not rely upon the Harris '464 reference are still relevant.

The gist of appellants' argument with respect to the obviousness rejections is that the prior art did not disclosed "all four isomer". As it was explained that racemization of duel

chiral center compounds gives *four isomer in thermodynamic mixture* is prima facie and is well known to one having ordinary skill. Although for such well known fact, the examiner did not have to elaborate, three references supporting such conclusion is hereby supplied for applicants' information. The Gao et al. reference (*exhibit C)* explicitly provided state of the art statement that "...racemization of the 'unwanted' enantiomer allowing its recycling.....is widely used in industry" (see p.197), thus, prima facie. The Shimoju et al. *(exhibit D)* or Beausoleil et al. *(exhibit E)* references disclosed that upon racemization of a two chiral center compound, a "thermodynamically equilibriaum" mixture of all four enantiomer will result (see Shimoju abstract, 99.5:0.5 mixture of DL-threo and DL erythro, i.e. all four isomers, see Beausoleil et al. p.9451 right column last six lines, ...treatment of(2S,5R)-5-tert-butylproline with acetic anhydride in acetic acid at 50oc conditions previously used ot racemize l-proline, provided a 3;1 cis-trans ration of diasteromers, and the CA 126 showing the structure of the diastereomers being all four combination). The prior art of record, although did not use Appelants' term " all 4 isomer" does not mean they are not all four isomers a mixture of epimers or misture of DL threo and DL erythro, must include four diasteriomers just as structurally delineated for the Beausoleil reference.

Therefore, to the extend the process is for the "disclosed" process of employing the unwanted *l-threo* methylphenidate to be racemized into a thermodynamic mixture of stereoisomeers, a prima facie obviousness has been established as delineated in the rejections. As for the non-disclosed subject matter in the claims, Appellants' argument that there is sufficient teaching can not overcome the issue. Appellants must find support for the claims that *l-threo* upon racemization will form none thermodynamically equilibrium mixture or the *d-threo* will form the thermodynamically equilibrieum mixture instead of all for in roughly equal amount.

Attorney's own delineation of theory without factual support can not be given weight especially the theory was based on that racemization of two chiral center is challenging. Just because it is challenging provides no factual evidence that it is not the innate nature well known in the field.

(C) To the extend that the instant claims are drawn to the scope of racemization of unwanted *l-threo* methylphenidate to a thermodynamic mixture of stereoisomeers in which

equilibrium may favour the *threo* isomer, the result is that undesired enantiomer is converted predominantly into the racemate of the threo isomer to be reintroduced into the resolution, the prima facie obviousness over the issued claim 1 of US 6,121,453 in view of Miller CA 94, Barry CA 119 or Miller US 4,254,261 for claims 1-6, and 8, the same argument of section (b) would also be applicable here and incorporated by reference.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Celia Chang
Primary Examiner
Art Unit 1625

June 22, 2005

Conferees

James O. Wilson, SPE 1623

Samuel A Barts, Primary examiner AU 1621

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